spinel, were the most likely source of the absorption, but a spinel-rich surface due to igneous processes could not be ruled out.

In a study that should be the template for future analyses of asteroids because of its combination of telescopic observations, meteoritic characterization, and spectral modeling, Sunshine *et al*. can now precisely link spinel-rich asteroids and CAIs. A visible spectroscopic survey of more than 1000 asteroids (*6*) identified possible spinel-rich objects in the visible-wavelength region due to their strongly reddish (reflectance increasing with increasing wavelength) spectra below ~0.75 μm and their featureless flat spectra from ~0.75 to 0.92 μm. Near-infrared measurements using SpeX (*7*), a medium-resolution infrared spectrograph located at the NASA Infrared Telescope Facility on Mauna Kea, found that these objects had the strong absorption characteristic of spinel. To determine the best compositional analog for these asteroids, CAIs and CAI-free matrix material from the CV chondrite Allende were separated out and characterized. Spectral modeling of the components was then done to best match the spectra of the asteroids and to narrow down the mineralogical interpretation.

One unanswered question is why these asteroids did not melt, which would have obliterated the spectral signature of the CAIs. If these asteroids contained the typical, initial $^{26}Al/^{27}Al$ ratios found in CAIs, their high aluminum contents should have caused melting. Perhaps these objects contained much lower abundances of $^{26}Al/^{27}Al$ and therefore constitute evidence for heterogeneous distribution of ^{26}Al in the solar nebula, or perhaps they contained very high abundances of ice (*8*) that acted as a buffer against full-scale melting and differentiation.

Sample return from an asteroid has been attempted only by the Japanese Hayabusa mission (*9*) from a near-Earth object (NEO), whereas the objects identified by Sunshine *et al.* reside in the main asteroid belt. If a spinel-rich NEO can be identified, it surely would be an attractive target for a sample return mission: obtaining for laboratory analysis some of the most primitive material still remaining in the solar system.

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CELL BIOLOGY

A One-Sided Signal

Changes in the distribution of a lipid within the plasma membrane affect normal cell function and virus infection.

Gregory D. Fairn and Sergio Grinstein

Lipids are increasingly recognized as essential for cells to transduce signals. Phosphoinositides—the phosphorylated derivatives of the membrane lipid phosphatidylinositol—control diverse cellular processes, including cell proliferation and survival, cytoskeletal organization, and vesicle trafficking. Similarly, the membrane lipid phosphatidylserine is key to initiating processes as important and dissimilar as blood coagulation and the clearance of dead cell remnants (apoptotic bodies). Defects in phosphatidylserine metabolism can lead to serious disorders including Scott's syndrome (a rare hemorrhagic disease) and autoimmune diseases such as systemic lupus erythematosus (*1*). Yet despite its importance, little is known about how phosphatidylserine functions during signal transduction. On pages 528 and 531 of this issue, Darland-Ransom *et al.* (*2*) and Mercer and Helenius (*3*) provide new insights into the biology of phosphatidylserine and reveal an unappreciated role in viral infection.

Unlike other phospholipids, the signals conveyed by phosphatidylserine do not entail metabolic conversion but are instead encoded by its subcellular localization. Phosphatidylserine is enriched in the plasma membrane. In healthy cells at rest, virtually all the phosphatidylserine is found in the inner leaflet of this lipid bilayer, where it serves as a molecular beacon for proteins that contain a structural motif called the C2-domain. Moreover, because phosphatidylserine is very abundant (≥20 mol % of the inner leaflet) and is anionic, it contributes substantially to the negative charge of the cytoplasmic face of the plasma membrane and promotes the recruitment of positively charged, polycationic proteins.

The mechanism that generates the striking asymmetry in the transmembrane distribution of phosphatidylserine has been debated extensively, but recent evidence suggests that a class IV P-type ATPase may be the long-sought enzyme (aminophospholipid translocase) that maintains this unequal distribution in the membrane bilayer (*4*, *5*). However, because the mammalian genome encodes at least 14 potential class IV ATPases, definitive genetic confirmation has been lacking. The likelihood that multiple isoforms of this lipid translocase (ATPase) would display redundant function has made removing or silencing the endogenous encoding genes in mammalian cells a daunting task. To circumvent this complication, Darland-Ransom and colleagues took advantage of the model nematode *Caenorhabditis elegans*, which contains only six homologs of these ATPases, also referred to as transbilayer amphipath transporters. Systematic gene silencing using RNA interference revealed that only the ATPase encoded by the gene *tat-1* is required to maintain phosphatidylserine asymmetry. Furthermore, cells that exposed phosphatidylserine on the outer (exofacial) leaflet of their plasma membrane, due to the elimination of *tat-1*, were subject to phagocytosis (internalization) by other cell types, even though the engulfed cells were not overtly undergoing cell death (apoptosis). Interestingly, the phagocytosis of cells exposing phosphatidylserine at the outer surface of their plasma membrane was not exhaustive and appeared to be random. This raises the possibility that engagement of cell surface receptors for phosphatidylserine, such as PSR-1 in *C. elegans* or Tim-1 and Tim-4 in mammalian cells (*6*), may not suffice to trigger phagocytosis, and that other signals

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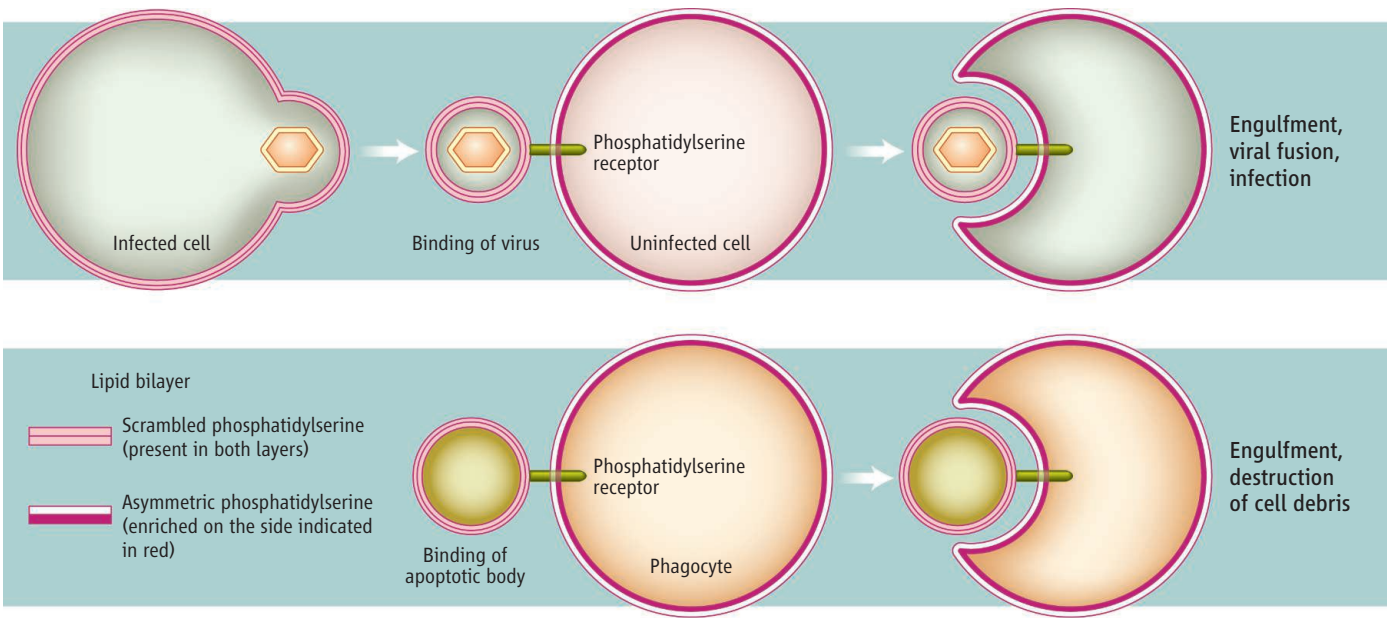
may contribute to the removal of apoptotic cells. In this regard, the cell surface protein CD36 recognizes oxidized forms of the phospholipid (*7*). A second alteration, such as the oxidation of exofacial phosphatidylserine, may be required for effective clearance of apoptotic bodies.

As reported by Mercer and Helenius, loss of phosphatidylserine asymmetry in the plasma membrane is also important for some viral infections. Like other viruses with a lipid bilayer coating, vaccinia virus acquires its membrane envelope as it buds off of the infected host cell. Because the infected cells undergo apoptosis, and thus experience scrambling of plasma membrane lipids, the budding virus also acquires an envelope that exposes phosphatidylserine on its external surface (see the figure). The authors found that, although not required for the virus to bind to the surface of the host cell, the presence of exofacial phosphatidylserine is required for viral entry. The nature of the internalization pathway is particularly intriguing because like other poxviruses, vaccinia virus is large (≥200 nm in diameter), exceeding the size accommodated by endocytosis, the engulfment process that uses specialized minute invaginations to internalize only a small area of the cell surface. Using a series of pharmacological agents, the authors showed that vaccinia enters cells by a process akin to macropinocytosis, a less specific internalization process that is more generally involved in the uptake of surrounding fluids. The sensitivity of vaccinia entry into cells to inhibitors of tyrosine kinases suggests the involvement of a transmembrane receptor for phosphatidylserine, as well as the existence of separate binding determinants on the receptor for the virus and for phosphatidylserine. This is consistent with a "tether and tickle" mechanism in which a separate attachment site is required for phosphatidylserine receptors to effectively bind and internalize apoptotic cells (*8*). The involvement of phosphatidylserine may not be limited to infection by vaccinia viruses. Papuamide B, a natural compound with anti-HIV properties, also binds to phosphatidylserine (*9*). It is therefore conceivable that HIV similarly requires phosphatidylserine for infection and that papuamide B interferes by occluding the lipid on the viral surface. The role of phosphatidylserine in the entry of HIV and other viruses will surely be explored in greater detail now.

The site(s) where membrane phosphatidylserine asymmetry is generated merit consideration. In eukaryotic cells, phosphatidylserine is synthesized primarily on the cytosolic aspect of the endoplasmic reticulum, an organelle through which secreted proteins pass. However, probes for phosphatidylserine failed to detect significant amounts of this lipid on the cytosolic surface of the endoplasmic reticulum or of the Golgi complex, another organelle of the secretory pathway (*10*, *11*). It is possible that phosphatidylserine fails to accumulate in the secretory pathway organelles because it is rapidly exported through this pathway following its biosynthesis. It may also be that newly synthesized phosphatidylserine is preferentially translocated to the luminal leaflet of these organelles, and thus is inaccessible to specific probes (*10*, *11*). Accordingly, the few studies analyzing phosphatidylserine sidedness in vesicles derived from the endoplasmic reticulum suggest that a vast majority of the lipid is in the luminal leaflet of the membrane (*12*). If these observations are validated, phosphatidylserine and other aminophospholipids could initially be delivered to the external aspect of the plasma membrane upon secretion, and would have to be rapidly "flipped" inward by specific enzymes (flippases). This speculation is lent some credence by the observations that phosphatidylethanolamine accumulates transiently within the membrane of yeast at sites of localized exocytosis and that this effect is accentuated when plasma membrane flippases are inactive (*13*).

Asymmetry in the distribution of plasma membrane phosphatidylserine clearly has functional importance, and the asymmetry may extend to other organelles. Yet our



Flipping lipids. A cell undergoing apoptosis exposes phosphatidylserine at its cell surface, a signal for a phagocytic cell to engulf the dying cell (or smaller pieces of the dying cell, called apoptotic bodies). Similarly, in the late stage of vaccinia virus infection, a host cell undergoes apoptosis and externalizes phosphatidylserine in its plasma membrane. A virus budding from this cell thus acquires a membrane envelope that exposes phosphatidylserine on its outer surface. This lipid serves as a signal for viral uptake by a noninfected cell through a mechanism similar to macropinocytosis.

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understanding of the molecular mechanisms that generate and maintain phosphatidylserine asymmetry is still in its infancy. The recent identification of phosphatidylserine-specific receptors and the development of genetically encoded biosensors to detect phosphatidylserine in live cells will accelerate discovery in this field.

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CLIMATE CHANGE

Carbon Crucible

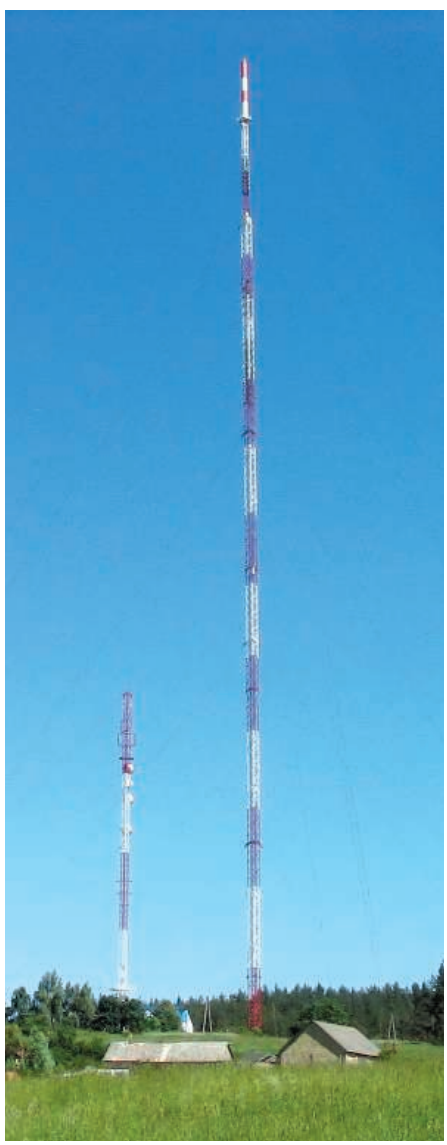
What are the data and modeling requirements for gauging the success of mitigation strategies in reducing greenhouse gas emissions?

Melinda Marquis[1,2*] and Pieter Tans[2]

Atmospheric measurements show that the carbon dioxide (CO_2) concentration in the atmosphere is currently ~385 parts per million (ppm) and rising fast. But this value is a global average that tells us nothing about the regional distribution of greenhouse gas emissions. As the world embraces myriad mitigation strategies, it must gauge which strategies work and which do not. Gaining such understanding will require a greenhouse gas monitoring system with enough accuracy and precision to quantify objectively the progress in reducing emissions, including regional efforts like those in California, New England, and elsewhere.

The current sparse network of observation sites across North America and elsewhere allows us to resolve annual continental fluxes of CO_2. But successful mitigation requires fluxes to be resolved within much smaller regions—on the order of the size of a European country such as France or a U.S. state such as Kansas. Current ground-based measurement technology can provide the required precision, but the number of measurements is insufficient. Data are collected by numerous agencies around the world, yet an integrated system is needed that uses all available data and ensures rigorous quality control for data collection and data analysis.

A powerful way to use all these data is in a data assimilation system, which combines diverse (and often sparse or incomplete) data and models into a unified description of a physical/biogeochemical system consistent with observations. Components of such systems include models of terrestrial photosynthesis (removal of CO_2, called a sink) and respiration (a source of CO_2), models of ecosystem emissions and uptake of other greenhouse gases, models of gas exchange between atmosphere and oceans, and models of gas emissions from wildfires—all grounded in observations.



The advantages of height. Atmospheric measurements are made on the tall tower (300 m). The tower, located near Bialystok in eastern Poland, is part of the CarboEurope tall tower network. Similar networks exist in North America and more sparsely in other parts of the world.

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The current grid scale for such assimilation systems—such as CarbonTracker, the first data assimilation system to provide CO_2 flux estimates (*1*, *2*)—is limited to ~100 km or larger, primarily due to computer resource limitations. Currently sparse atmospheric greenhouse gas data force us to make the assumption that source variations are coherent over very large spatial scales. More observation sites would make the systems more strongly data-driven. Data assimilation systems also need more refined estimates of fossil fuel emissions, and better process understanding to provide greater detail in emission patterns. Lastly, better models of atmospheric transport will increase the resolution and decrease biases of the data assimilation system. Our ability to distinguish between distant and nearby sources and sinks is limited by how accurately transport models reflect details of the terrain, winds, and atmospheric mixing near the observation sites.

National emissions inventories (which are required by the U.N. Framework Convention on Climate Change) are key data sets for assimilation systems. Inventories are mostly based on economic statistics, which are used to estimate how much of each greenhouse gas enters or leaves the atmosphere (*3*). They are reasonably accurate for CO_2 from fossil fuels (within ~10%) in many developed countries but less so in developing countries and on regional scales. Inventory emission estimates are much less reliable for other CO_2 sources, such as deforestation, and for other major greenhouse gases; for example, the contributions of natural wetlands, rice farming, and cattle to the global methane

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